Whole-genome sequencing suggests a chemokine gene cluster that modifies age at onset in familial Alzheimer's disease.

Journal: Mol Psychiatry

Publication Year: 2015

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PubMed link: 26324103

Funding Grants: The UCSB Laboratory for Stem Cell Biology and Engineering

Public Summary:
We have sequenced the complete genomes of 72 individuals affected with early-onset familial Alzheimer's disease caused by an autosomal dominant, highly penetrant mutation in the presenilin-1 (PSEN1) gene, and performed genome-wide association testing to identify variants that modify age at onset (AAO) of Alzheimer's disease. Our analysis identified a haplotype of single-nucleotide polymorphisms (SNPs) on chromosome 17 within a chemokine gene cluster associated with delayed onset of mild-cognitive impairment and dementia. Individuals carrying this haplotype had a mean AAO of mild-cognitive impairment at 51.0 ± 5.2 years compared with 41.1 ± 7.4 years for those without these SNPs. This haplotype thus appears to modify Alzheimer's AAO, conferring a large (~10 years) protective effect. The associated locus harbors several chemokines including eotaxin-1 encoded by CCL11, and the haplotype includes a missense polymorphism in this gene. Validating this association, we found plasma eotaxin-1 levels were correlated with disease AAO in an independent cohort from the University of California San Francisco Memory and Aging Center. In this second cohort, the associated haplotype disrupted the typical age-associated increase of eotaxin-1 levels, suggesting a complex regulatory role for this haplotype in the general population. Altogether, these results suggest eotaxin-1 as a novel modifier of Alzheimer's disease AAO and open potential avenues for therapy.

Scientific Abstract:
We have sequenced the complete genomes of 72 individuals affected with early-onset familial Alzheimer's disease caused by an autosomal dominant, highly penetrant mutation in the presenilin-1 (PSEN1) gene, and performed genome-wide association testing to identify variants that modify age at onset (AAO) of Alzheimer's disease. Our analysis identified a haplotype of single-nucleotide polymorphisms (SNPs) on chromosome 17 within a chemokine gene cluster associated with delayed onset of mild-cognitive impairment and dementia. Individuals carrying this haplotype had a mean AAO of mild-cognitive impairment at 51.0 +/- 5.2 years compared with 41.1 +/- 7.4 years for those without these SNPs. This haplotype thus appears to modify Alzheimer's AAO, conferring a large (~10 years) protective effect. The associated locus harbors several chemokines including eotaxin-1 encoded by CCL11, and the haplotype includes a missense polymorphism in this gene. Validating this association, we found plasma eotaxin-1 levels were correlated with disease AAO in an independent cohort from the University of California San Francisco Memory and Aging Center. In this second cohort, the associated haplotype disrupted the typical age-associated increase of eotaxin-1 levels, suggesting a complex regulatory role for this haplotype in the general population. Altogether, these results suggest eotaxin-1 as a novel modifier of Alzheimer's disease AAO and open potential avenues for therapy.